REMARKS

Claims 6-8, 11-16 and 20-23 are pending in the application. Claim 22 has been amended to correct minor typographical error.

Rejection under judicially created doctrine of obviousness-type double patenting

Claims 20, 21 and 23 stand rejected over various claims of co-pending application 09/713188. If conflicting claims are still present when the present application is allowed, Applicants will submit a terminal disclaimer over the '188 application.

Rejection under 35 U.S.C. 112, first paragraph

Claims 6-8, 11-16, 20- 23 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse.

A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In the present application, methods for making and using the claimed subject matter are described in general terms on pages 21-35. These are followed by over 300 examples of specific compounds as well as several experimental procedures for evaluating compounds for VLA-4 antagonist activity. The specification thus contains ample teachings to enable a skilled artisan to practice the claimed invention. The Examiner, nevertheless, still contends that "undue experimentation" is required to practice the claimed invention stating that "VLA-4/ligand interactions are very specific, and very exacting, and above all, the structural features necessary for antagonism cannot be predicted." The Examiner cites Dutta, Arrhenius, Komoriya, Haworth, Haubner and Lin as purportedly supportive of his position.

Of the six references cited, three, viz. Dutta, Arrhenius and Lin, report structure/activity relationships (SAR) of potential VLA-4 antagonists. Dutta teaches that cyclic peptides containing the tetrapeptide sequence Xaa-Leu-Asp-Val are potent inhibitors of VLA-4-mediated cell adhesion (where Xaa is Ile or a replacement amino acid), and shows a large number of

compounds with diverse structures within the series as being active in *in vitro* assays. Similarly, Arrhenius shows numerous examples of N-terminal capped di- and tripeptides containing Leu-Asp as active VLA-4 antagonists. Lin discloses phenylacetyl-Leu-Asp compounds with various substituents on the phenylacetyl group and varying peptide chain lengths as $\alpha 4\beta 1$ inhibitors. The remaining three cited references are not SAR studies. Komoriya establishes the tripeptide sequence Leu-Asp-Val as the minimal active amino acid sequence essential for the recognition of fibronectin by the $\alpha 4\beta 1$ integrin receptor. Haworth is an in-depth study of the peptide c[Ile-Leu-Asp-Val-$NH(CH_2)_5CO$], while in passing discloses that the number of methylene affects VLA-4 antagonist activity. Haubner relates to $\alpha v\beta 3$ integrin and it is unclear how this reference is relevant to the present case.

In discussing Dutta, Arrhenius and Lin the Examiner chooses to focus on a few outlier compounds in each series while ignoring data showing that the majority of the compounds sharing a particular structural feature (e.g., the tetrapeptide sequence of Dutta, capped di- and tripeptides of Arrhenius, and phenylacetyl capped Leu-Asp of Lin) in fact do exhibit the desired biological activity. The teachings of Dutta, Arrhenius and Lin demonstrate that within a compound series a wide structural variation may be tolerated without abolishing biological activity. These references therefore do not support the Examiner's assertion; rather, they undermine it. Given that the Examiner has not advanced adequate scientific reasoning and/or evidence as to why an enablement rejection is appropriate, Applicants respectfully urge that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, first paragraph.

Applicants note the Examiner's suggestion to delete the term "pharmaceutical" from claim 20. However, since there is no explanation as to why the deletion is required, Applicants have not complied with the suggestion.

Rejection under 35 U.S.C. 112, second paragraph

Claim 22 stands rejected as being indefinite for for containing a unmatched "right-hand" bracket in the 14th compound listed. Claim 22 has been amended to remove said bracket obviating the rejection. Withdrawal of the rejection is requested.

In view of the amendments and remarks presented above Applicants believe the application is in condition for allowance. An early favorable action is respectfully urged.

Respectfully submitted,

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